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Glick et al., "Psychopharmacologic treatment strategies for depression, bipolar disorder and schizophrenia", **Ann. Internal Medicine**, (134, No. 1, 47-60)(2001). **I need the exact date of publication.** → January 2, 2001

Von Degner et al., "New antidepressant drugs: spectrum and clinical relevance of side effects", **Muench. Med. Wochenschr.** (142, No. 49-50, 35-40) (2000).

Zanni et al., "Combined treatment with reboxetine and antipsychotic drugs on amphetamine-induced locomotion and striatal fos expression", **Society for Neuroscience Abstracts**, Vol. 27, No. 2, pp. 2586 (2001). **I need the exact date.**

Thank you.

Phyllis Spivack
1614

308-4703

Psychopharmacologic Treatment Strategies for Depression, Bipolar Disorder, and Schizophrenia

Ira D. Glick, MD; Trisha Suppes, MD, PhD; Charles DeBattista, MD; Rona J. Hu, MD; and Stephen Marder, MD

Patients with serious psychiatric disorders are frequently treated by primary care physicians, who may have difficulty keeping up with recent advances in psychiatry. This paper presents an updated synopsis for three major psychiatric illnesses: major depression, bipolar disorder, and schizophrenia. Current definitions, updated diagnostic criteria, short- and long-term treatment strategies with algorithms, and special challenges for the clinician are discussed for each of these illnesses. On the basis of each illness's distinct characteristics, five treatment principles are emphasized: 1) Treatment strategies should be long-term and should emphasize adherence, 2) treatment choice should be empirical, 3) combinations of medications may be helpful, 4) a combination of psychosocial and pharmacologic treatments may be more useful than either alone, and 5) the family or "significant others" as well as a consumer organization need to be involved. Some of the new directions in clinical research to refine these strategies and meet these challenges are also described.

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Patients with major psychiatric illnesses are often treated first, and sometimes exclusively, by family physicians and internists. Because the diagnosis and treatment of these disorders have changed profoundly in two decades, it may be difficult for specialists outside of psychiatry to keep informed (1–3). This, in turn, could lead to underdiagnosis and undertreatment. We therefore provide an updated synopsis for three important psychiatric disorders: major depression, bipolar disorder, and schizophrenia. Much of this information is not covered in consensus guidelines (4–6) or comprehensive reviews of these disorders (7), which are circulated minimally outside psychiatry and are not usually followed even when available (8).

We describe updates in the diagnosis of each disorder and, most important, illness characteristics and treatment principles that underlie current strategies for short- and long-term psychopharmacologic treatment. These differ markedly from past strategies because they incorporate new interventions and medications on the basis of data from controlled studies (Table 1). In the short term, this means assessing a new patient and clarifying the diagnosis while rapidly initiating treatment to relieve symptoms. In the long term, this means reviewing current patient status to avoid relapse and to maintain the patient at the highest level of functioning possible. While our article focuses on psychopharmacology, it is now established that medications combined with individual and family psychotherapeutic interventions are helpful. We will not cover details of drug selection, dosing, or underlying biology, all of which are discussed in textbooks and consensus guidelines (4–6). For each condition, preferred medications (Table 2) and algorithms (Figures 1 to 5) reflect general principles of drug management.

DEPRESSION

Updates in Definition and Diagnosis

Current research in the diagnosis of depression has focused on special populations and on identifying subtypes that may respond differently to treatment. Major depression is defined as having at least five symptoms during the same 2-week period, with marked change in function. At least one of the symptoms must be depressed mood or loss of interest or pleasure. In addition, changes in at least three of the following must be observed: weight, sleep, activity level, energy, ability to think or concentrate, or suicidal ideation (9). Subtypes being investigated include depression associated with psychotic symptoms, atypical features, or seasonal patterns (which may respond to bright-light therapy). A major diagnostic task is differentiating major depression from depressed states secondary to life stress, alcohol or drugs, medical illness, or bereavement (although depressive symptoms must be treated regardless of cause). Careful history, including family history, helps clarify the differential diagnosis, but clinicians should remember that depression is not a rare disorder. Lifetime prevalence is estimated at 15% and at perhaps 25% in women.

Table 1. **Characteristics of Psychiatric Illnesses and Indicated Treatment Principle**

Characteristic of Illness	Treatment Principle
Chronic	Strategies should be long term and emphasize adherence
Symptoms related to diverse pathophysiologic processes	Choice should be empirical
Psychopathology in more than one area	Combinations of medications may be helpful
Influenced by life events and environment	A combination of psychosocial and pharmacologic treatments may be more useful than either alone
Affects cognition and therefore adherence	The family or "significant others" as well as a consumer organization need to be involved*

* It is important to remember that there are many other reasons for the family to be involved.

Updates in Short-Term Strategies

Choice of treatment for depression has changed substantially over the past two decades (Table 2). Formerly, all but the most severe cases of depression were treated first with psychotherapy alone. Currently, only mild to moderate depression may be treated with psychotherapy alone; even then, antidepressants may be equally effective (10). Psychotherapy itself has shifted from psychoanalytic to more short-term, cognitive–behavioral, or dynamic supportive therapy (11), the effects of which may outlast discontinuation of treatment.

The short-term treatment of depression changed dramatically as new medications became available. In part because older tricyclic antidepressants were dangerous in overdose, physicians were reluctant to treat depression with medication. Although new medications are much safer in overdose, allowing earlier and more aggressive treatment, depression continues to be underrecognized and undertreated (1).

Short-term antidepressant therapy has several goals. The first is to relieve suffering. While antidepressants may take weeks to achieve maximum benefit, improvements in sleep, anxiety, and agitation may occur earlier. A second goal is to instill hope. Prescribing an antidepressant may in itself send the message that patients have a treatable illness. Most patients regard this as positive; others, however, may resist the implication that they are "mentally ill." A third goal is to improve functioning. Because a latency of response is seen with all antidepressants, this may take 4 weeks or longer.

If no response occurs after 4 weeks of therapy with a therapeutic dose, the dose is usually increased. This strategy may be useful even with serotonin reuptake inhibitors (SSRIs), which were considered to have a flat dose–response curve (12). Titration to two thirds of the maximum dose can be reasonable if tolerated by the patient. No response at a higher dose should prompt consideration of switching antidepressants. In the past, little evidence supported changing from one tricyclic antidepressant to another; now, better evidence indicates that switching to another class of agents may result in a 50% or greater response (13). Serotonin reuptake inhibitors are chemically heterogeneous, and data suggest justification for switching from one to another.

Despite general agreement in the clinical community that 4 weeks is an adequate trial for an antidepressant, it is important to support this with research. Some studies recommend 6 to 8 weeks at full dose (14). Recent data on fluoxetine, however, do not indicate that a fixed-dose trial exceeding 4 weeks significantly improved response (15). One could conclude that 4 weeks at a therapeutic dose is probably adequate but that higher doses may improve response rate (12).

Newer strategies in choosing antidepressants consider both patient and drug variables. Patient variables include sex, age, and depression subtype. Sex can affect

Table 2. **Drugs Used in Depression, Bipolar Disorder, and Schizophrenia**

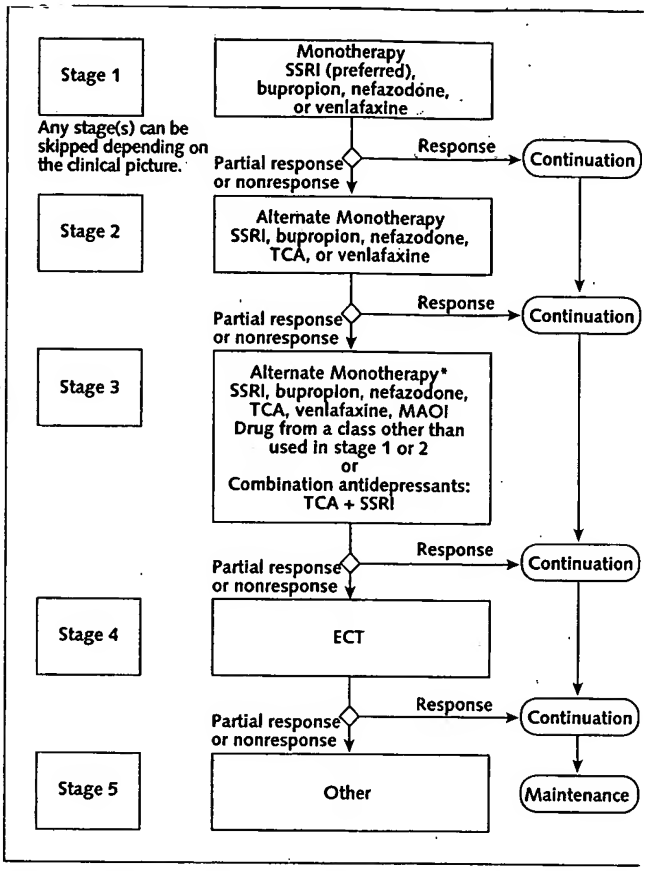
Antidepressants	Typical Antipsychotics	Atypical Antipsychotics	Mood Stabilizers
Amitriptyline	Chlorpromazine	Clozapine	Lithium
Amoxapine	Thioridazine	Olanzapine	Valproic acid
Bupropion	Mesoridazine	Quetiapine	Carbamazepine
Citalopram	Fluphenazine	Risperidone	Gabapentin
Clomipramine	Perphenazine	Ziprasidone	Lamotrigine
Desipramine	Trifluoperazine		
Doxepin	Thiothixene		
Fluoxetine	Haloperidol		
Fluvoxamine	Loxapine		
Imipramine	Molindone		
Isocarboxazid	Pimozide		
Maprotiline	Droperidol		
Mirtazepine			
Nefazodone			
Nortriptyline			
Paroxetine			
Phenelzine			
Protriptyline			
Reboxetine			
Sertraline			
Tranylcypromine			
Trazodone			
Trimipramine			
Venlafaxine			

response to different classes of antidepressants. Large meta-analyses show that men may have better response to and tolerance of tricyclic antidepressants (16) and that women may better respond to and tolerate select SSRIs (17). Advancing age can affect hepatic metabolism and renal clearance, increasing the risk for toxicity to all antidepressants, particularly tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Geriatric patients are especially sensitive to anticholinergic effects of such tricyclic antidepressants as amitriptyline and often cannot tolerate MAOIs because of orthostatic hypotension. Older patients often take several medications that can interact. Although serious interactions are less likely with newer agents, most SSRIs competitively inhibit the CYP2D6 isoenzyme that metabolizes class 1C antiarrhythmics, increasing serum levels and potentially producing toxicity. Fluoxetine, which has broader interactions than other SSRIs, has a metabolite whose long half-life makes it a threat even after discontinuation.

Prevailing clinical opinion of the controlled data suggests that all antidepressants have equal efficacy, approximately 60% to 70% in any given trial. In subtypes of depression, however, real differences are discernible. Atypical depression with mood reactivity, hypersomnia, and hyperphagia responds better to MAOIs than to tricyclic antidepressants (18). For premenstrual mood symptoms, SSRIs are more effective than tricyclic antidepressants (19). Psychotic depression had only a 30% to 40% response rate to tricyclic antidepressants in several trials but may have a 70% response rate to the tetracyclic amoxapine (20). However, its metabolite is a neuroleptic that may cause tardive dyskinesia. In standard treatment, a neuroleptic is combined with an antidepressant and electroconvulsive treatment is used as a backup. New "atypical" antipsychotics (serotonin–dopamine antagonists), particularly olanzapine, are promising as monotherapy (21).

Drug-related variables include safety in overdose, a safe side effect profile, and cost (22). Because tricyclic antidepressants and MAOIs are available in generic forms and are less expensive, third-party payers formerly insisted that they be tried first. However, the total cost of antidepressant treatment is complex. Tricyclic antidepressants require screening electrocardiography in older patients, serum level evaluations, and possibly more frequent office visits for side effects and premature discontinuation of drug therapy. A tricyclic antidepressant

Figure 1. **Strategies for the treatment of major depressive disorder without psychotic features.**



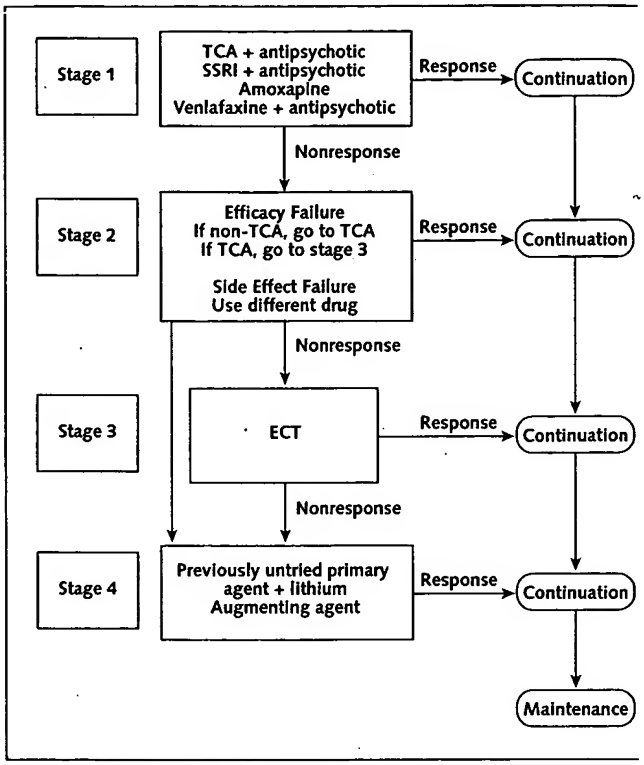
ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant. *Consider TCA or venlafaxine if not tried. Reproduced from J Clin Psychiatry. 1999;60:142-56.

overdose is prohibitively expensive in both economic and human terms. With these costs included, tricyclic antidepressants seem more costly than newer antidepressants (23).

Updates in Long-Term Strategies

The long-term goal in treating depression is preventing relapse and recurrence. Concepts undergoing revision include how long to continue medication treatment and when to augment it. Overwhelming evidence now shows that major depression tends to recur, often within 2 years; in at least 75% of patients, it recurs within 10 years. Premature termination of medical therapy apparently increases risk for relapse. Evidence suggests that a minimum course of 6 months reduces this

Figure 2. **Strategies for the treatment of major depressive disorder with psychotic features.**



ECT = electroconvulsive therapy; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant. Reproduced from J Clin Psychiatry. 1999;60:142-56.

risk. However, depressive disorders are characterized by heterogeneity of outcome. Some patients may not have recurrences after their first depressive episode, a fact worth remembering for the clinician considering cautiously tapering medication in long-stabilized patients. Patients with two or more serious recurrences in 5 years or three serious lifetime recurrences should receive long-term antidepressant therapy.

Long-term antidepressant therapy seems to have a prophylactic effect. Frank and colleagues (24) found that patients with recurrent major depression who received imipramine for 3 years were four times more likely to stay depression-free than those who were randomly assigned to placebo after remission. Studies that lasted for approximately 1 year have supported a similar prophylactic effect of newer antidepressants, including fluoxetine, paroxetine, venlafaxine, and nefazodone. All antidepressants seem to be useful in the long term for preventing recurrence.

Although 60% to 70% of patients experience a significant response to a given antidepressant, fewer than 25% in a given trial become symptom-free. Residual symptoms can persist for months or years after a depressive episode resolves (25). Thus, adjunctive agents are frequently required to turn partial response into full response. The best-studied augmenting agents for major depression are lithium and triiodothyronine. More than 40 studies have examined lithium augmentation since it was initially reported by DeMontogny and coworkers (26). Low doses can achieve full response in approximately 50% of partial responders to all antidepressant classes tested. Response may occur within 72 hours (20), but it usually takes up to 6 weeks to attain maximum benefits. Thyroid supplementation, which has been studied for many years (27), may be useful for patients with partial response to antidepressants but is not as consistently effective as lithium. Other strategies include combining such antidepressants as trazodone, bupropion, or a tricyclic antidepressant with an SSRI or venlafaxine. Some anecdotal evidence supports the use of adjunctive stimulants, buspirone, and β-blockers.

Special Challenges and New Directions

The first major strategic challenge for depressive disorders is their well-documented undertreatment in medical settings, both psychiatric and nonpsychiatric (1). Key issues include inadequate dose and duration and potential bias against medication. When patients prematurely discontinue antidepressant therapy, direct health care expenditures increase substantially (22).

A related challenge, part of the traditional undertreatment of depression, has been the high risk for suicide by overdose on the medications prescribed to treat depression (28). Newer antidepressants reduce this risk: A recent review of more than 200 fluoxetine overdoses revealed no deaths and few complications (29). However, tricyclic antidepressant overdoses, with fatal arrhythmia, still account for several hundred suicides annually nationwide.

As depression becomes more safely and more widely treated, managing side effects becomes increasingly important and should be discussed with the patient and family. The tertiary amine tricyclic antidepressants are very anticholinergic, particularly in elderly persons. Significant orthostatic hypotension occurs with tricyclic

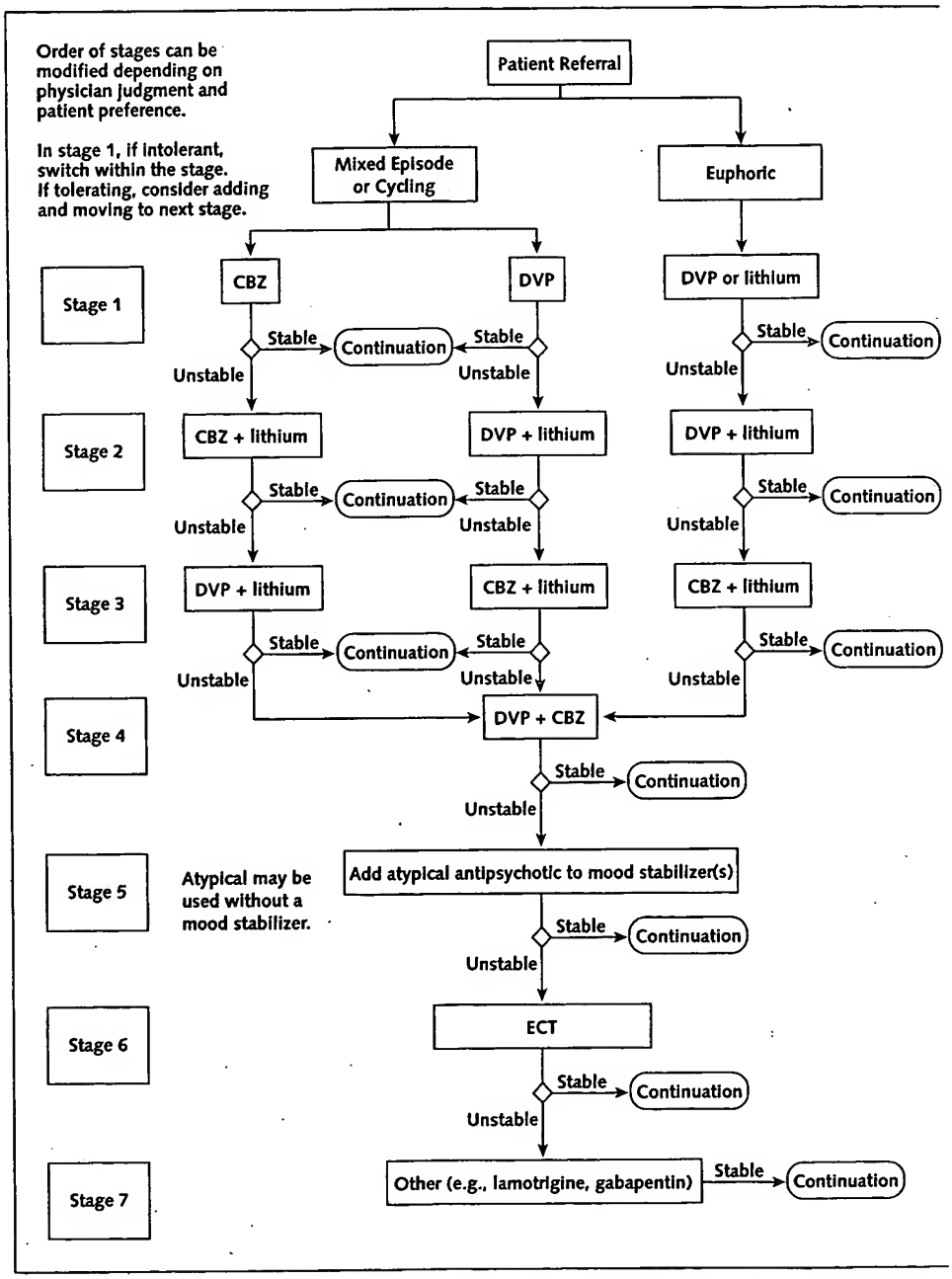
antidepressants, MAOIs, and trazodone but not with SSRIs and most newer agents. Although side effects of SSRIs tend to be milder, gastrointestinal and sexual side effects may be more common and can lead to discontinuation of drug therapy.

BIPOLAR DISORDERS

Updates in Definition and Diagnosis

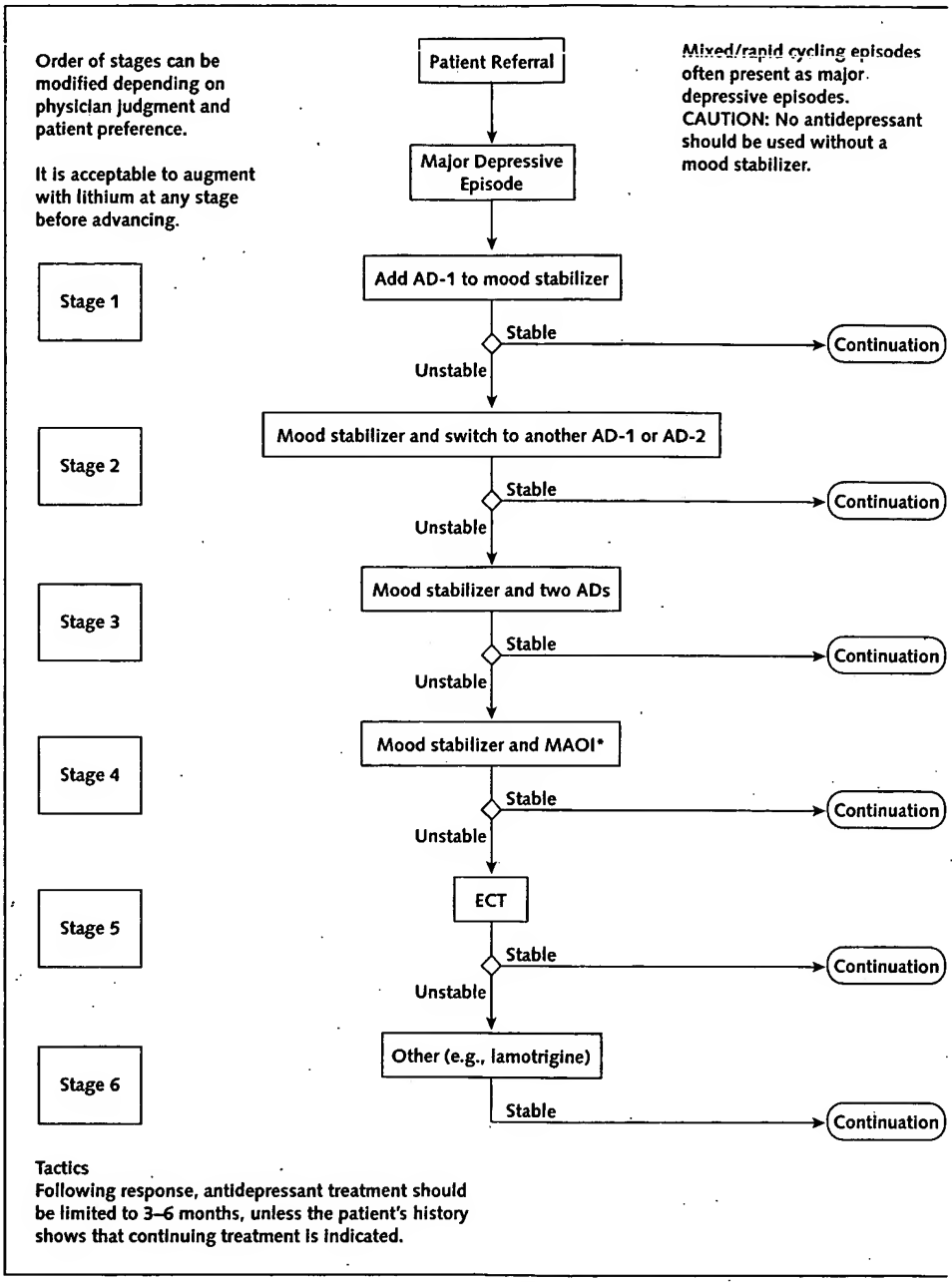
A paradigm shift in the diagnosis of bipolar (formerly manic-depressive) disorder occurred with the recognition of subtypes bipolar I and II. Patients with bipolar I

Figure 3. **Strategies for the treatment of manic/hypomanic episodes.**



CBZ = carbamazepine; DVP = divalproex sodium; ECT = electroconvulsive therapy. Reproduced from Journal of Practical Psychiatry and Behavioral Health. 1999;5:142-8.

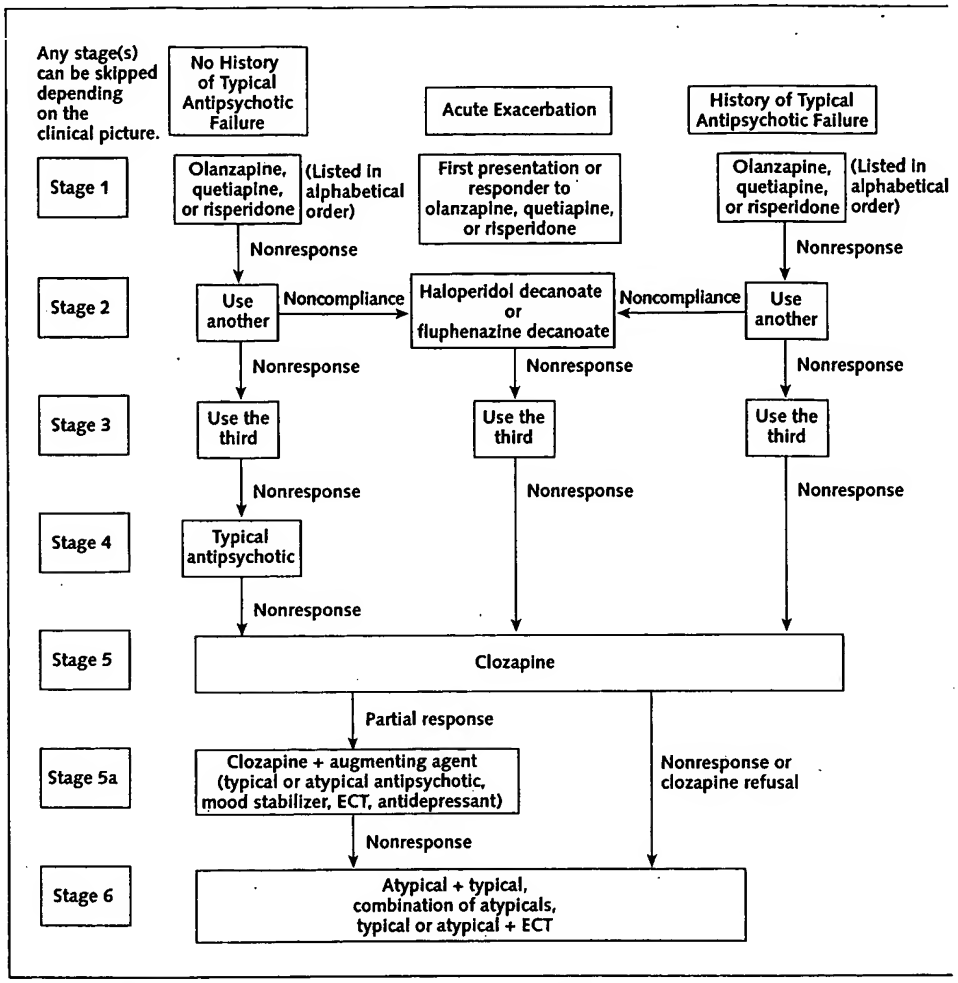
Figure 4. **Strategies for the treatment of major depressive episodes.**



AD = antidepressant; AD-1 = bupropion SR or selective serotonin reuptake inhibitor; AD-2 = venlafaxine or nefazodone; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor. Reproduced from Journal of Practical Psychiatry and Behavioral Health. 1999;5:142-8.

have a history of depression and mania, while those with bipolar II have depression and hypomania (mood elevations that are abnormal for the individual but do not seriously impair functioning or require hospitalization). Mania is defined as a distinct period of abnormally elevated, expansive, or irritable mood lasting at least 1 week, with such symptoms as grandiosity, decreased need for sleep, racing thoughts, or excessive involvement in activities that have a high potential for painful consequences (30). Patients with bipolar I may also experi-

Figure 5. **Strategies for the treatment of psychosis.**



ECT = electroconvulsive therapy. Reproduced from J Clin Psychiatry. 1999;60:649-57.

ence psychotic symptoms during unstable mood. Conservative estimates indicate that these disorders affect at least 1.4% of the population (31).

Differential diagnosis includes personality disorders, major depression, schizophrenia, substance abuse, and primary medical or neurologic conditions. Although some personality disorders can include rapid mood changes, irritability, and tumultuous relationships, in bipolar disorder these symptoms should remit between clear episodes and should generally respond to treatment. It is important to distinguish bipolar from unipolar major depression because this guides whether patients receive a mood stabilizer or an antidepressant alone. Similarly, a concomitant medical disorder, such as hyperthyroidism, changes treatment focus.

Lifetime prevalence of alcohol and substance abuse in patients with bipolar I may exceed 60% and may confound treatment efforts. Formerly, some clinicians believed that substance abuse would have to be addressed first, before the mood disorder. Current practice favors addressing both issues together, using mood stabilizers concurrently with substance use interventions (even for patients who deny a substance abuse problem).

Updates in Short-Term Strategies

The primary short-term goal is to decrease the severity and duration of manic or depressive episodes. Current evidence indicates that the more episodes a patient has experienced, the greater the likelihood of future

episodes. Because an accumulation of episodes may also have a cumulative negative effect on cognitive function (32), aggressive, early treatment is important. There are more medication choices now, and the drug of first choice has begun to shift away from lithium toward the anticonvulsants.

If a patient is manic or hypomanic, the goal of treatment is to decrease symptoms by using medications that have the fewest side effects. Drugs commonly used are lithium, anticonvulsants, typical and atypical antipsychotics, and benzodiazepines. For bipolar I disorder (classic acute mania), many clinicians may still regard lithium as the treatment of choice, but others prefer divalproex sodium (valproate). In bipolar II disorder, treatment guidelines support the use of anticonvulsants (especially valproate) or lithium, although more controlled trials are needed to compare active treatments. It is important to note that valproate is contraindicated in patients with substantial hepatic dysfunction and that carbamazepine is contraindicated in patients with intermittent porphyria or atrioventricular heart block. Current studies favor rapidly titrating to a full dose of valproic acid within 1 to 2 days; approximately two thirds of patients show significant improvement within 5 to 7 days (33), decreasing the need for adjunctive benzodiazepines and antipsychotics. Minimizing the use of traditional antipsychotic medications in acute mania can prevent tardive dyskinesia, to which bipolar patients may be especially susceptible. One double-blind, controlled study found that the benzodiazepine lorazepam was as useful as the antipsychotic haloperidol for managing extreme agitation (34). A new trend favors short-term therapy with atypical antipsychotics, which have an improved side effect profile and have decreased the use of older antipsychotics. In patients with mixed states—mania and depression simultaneously—studies indicate that anticonvulsants are more efficacious than lithium (35), particularly in patients with a history of closed head injury, substance abuse, or other neurologic impairments (36, 37).

Treating acute depression in bipolar patients improves quality of life and decreases risk for suicide, but controlled studies are still limited (38). Many patients with bipolar disorder may periodically need antidepressants, probably at the doses used for major depression; however, this may destabilize mood and cause mania. Therefore, antidepressants should always be added to a mood stabilizer and should never be used alone in patients with bipolar illness.

Other considerations in medication choice include suicide risk and onset of action. Research supports differences between lithium, valproate, and carbamazepine. Risk for suicide in bipolar patients is serious and has been estimated at approximately 15% among untreated or treated persons. New information strongly suggests that lithium decreases mortality rates in suicidal patients by acting on the serotonin system (39). One recent small open European study found that rates of suicide decreased among patients receiving lithium but not among those receiving carbamazepine (40). This finding, however, must be replicated in further studies. Medications differ in acute onset of action; anticonvulsants are faster than lithium (5 to 10 days vs. 10 to 14 days). Regardless of medication choice, however, it is important to use an adequate dose for an adequate period. Although individual psychotherapy in acute mania is of small benefit when insight and cognitive abilities are limited, family intervention and education improve outcome, especially in patients with moderate to severe mania (41)

Updates in Long-Term Strategies

Long-term treatment requires management of mood lability or instability between acute episodes. Current treatment paradigms strongly endorse continuing medication, even when symptoms remit, and are examining "rational polypharmacy"—using more than one medication. Periods of mood lability—including irritability, disturbed sleep, poor concentration, and impulsivity—need to be examined in the context of psychosocial precipitants, stress, and compliance. Decisions to adjust medications should take these factors into account.

A patient who becomes hypomanic despite medication adherence probably requires a change in treatment. Hypomania is now considered a highly unstable state that may lead to a manic or depressive episode. Since hypomania is commonly heralded by a decrease in sleep time, it is important to restore the usual number of hours. Options include use of benzodiazepines, higher doses of divalproex, or low doses of sedating antipsychotics. These are not necessarily long-term changes, and added drugs may be tapered after the patient's condition stabilizes.

Although the literature offers little guidance on using more than one agent simultaneously, this practice is common. Patients with severe bipolar illness often take two to four drugs. This raises the issue of excessive use of medication; however, preclinical data show that each medication has a different mechanism of action. At this time, bipolar illness is still a descriptive clinical syndrome probably caused by diverse, little-understood mechanisms (42).

Stabilizing mood and restoring the patient to functioning are essential (43). While mood stabilizers decrease manic symptoms, their antimanic efficacy may contribute to chronic low-grade depression. If a patient is experiencing mild depression, it is important to consider decreasing the mood stabilizer dose or adding a second mood stabilizer rather than automatically adding an antidepressant. Lithium, divalproex, and carbamazepine have been associated with an antidepressant effect in some case series and a depressive effect in others. Lithium has been most extensively studied and should be considered as an augmenting agent for depression as well as for mood stabilization.

Limited data suggest that tricyclic antidepressants are more likely to initiate a switch into mania than some other agents. Newer antidepressants, including SSRIs, bupropion, nefazodone, and venlafaxine, have become the first-line choices, partly because they have fewer side effects. One double-blind study and a replication of that study indicate that bupropion may be less likely than some antidepressants to cause switching (44), but other reports disagree (45). Older data support the efficacy of MAOIs in patients with bipolar disorders (46), but because these agents entail health risks and dietary restrictions, they are rarely tried first.

Long-term supportive psychotherapy for the patient and marital or family therapy for significant others (41) help maintain compliance and cope with the fear of relapse. While the acutely manic patient is often not able to participate in therapy, the periods between episodes are often times to solidify treatment alliances and gain insight on the illness.

Special Challenges and New Directions

Bipolar disorder is by nature an episodic illness with periods of euthymic mood alternating with periods of mania or depression. Because current mood stabilizers have a defined therapeutic range, often necessitate blood monitoring, and do not sufficiently treat all patients, new agents are being tried. For treatment-resistant patients in whom combination treatment with current mood stabilizers fails, atypical antipsychotics are being actively investigated. Studies show that clozapine has mood-stabilizing properties, particularly antimanic efficacy (47). Risperidone reportedly is helpful when used in conjunction with other mood stabilizers and may be a mild antidepressant (48). Olanzapine, an atypical antipsychotic, shows promise in bipolar disorder (49, 50) and is now the first antipsychotic to be approved by the U.S. Food and Drug Administration for treatment of acute mania with or without psychotic features. Quetiapine may also be useful, although controlled studies are currently lacking. The role of atypical antipsychotics in short-term and maintenance treatment is currently being studied in several controlled trials. New anticonvulsants with possible antidepressant effects include lamotrigine and gabapentin, which also have mild antianxiety properties (51), and lamotrigine (52). Reports are emerging about the latter's likely antidepressant and possible mood-stabilizing properties, but its use is limited by risk for serious rash if the dose is increased rapidly. Few controlled studies have focused on the systematic use of polypharmacy, but several are under way and should allow improvement of the guidelines soon.

SCHIZOPHRENIA

Updates in Definition and Diagnosis

Current understanding of schizophrenia, which emphasizes a biological cause, is a major shift from earlier concepts that blamed family communication styles. Lifetime prevalence is currently estimated at 1% to 1.5% in the general population. Although the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* continues to emphasize the presence of psychotic symptoms (delusions and hallucinations) as well as social and vocational impairment, the focus has broadened to include negative symptoms (flat affect, social isolation) and cognitive impairments frequently seen among patients with schizophrenia (53). Current research indicates that these cognitive and negative symptoms may have a greater impact on long-term prognosis than psychotic symptoms.

Differential diagnosis includes bipolar disorder and

substance abuse disorders. Schizophrenia and bipolar disorder can have many common features, but patients with schizophrenia primarily manifest disorders of thought rather than mood and have lower levels of social and vocational functioning between episodes. Although patients with bipolar disorder can have delusions during manic periods, their delusions tend to be grandiose to match their mood and should resolve when the mania resolves. Patients with schizophrenia tend to have more bizarre delusions (for example, involving aliens or microchip implants) that do not depend on their moods. Although patients with schizophrenia commonly abuse illegal drugs, a purely substance-induced psychosis should subside rapidly with cessation of use of the drug. Moreover, patients with schizophrenia do not commonly show the confusion and disorientation of acute substance-induced psychosis. Schizoaffective disorder, which combines both thought and mood symptoms, is less frequently diagnosed than in the past and is essentially treated like other types of schizophrenia.

Updates in Short-Term Strategies

In the acute phase, the primary goal is to reduce the most serious symptoms, including hallucinations, delusions, agitation, and disorganized thought and behavior. The mainstay of short-term treatment, regardless of whether the patient is hospitalized, is selecting an antipsychotic medication. Pharmacologic treatment has become more aggressive in the past two decades, and evidence suggests that delays in initiating antipsychotics may have long-lasting effects in worsening psychotic episodes and social adjustment (54). Even if a patient recovers without medications, the time spent in a psychotic state may adversely affect long-term outcome. Although schizophrenia is a chronic illness, evidence suggests that early antipsychotic treatment can improve outcome (55).

Selecting an antipsychotic has become more complex with the advent of newer agents (**Figure 5**). Before 1990, all antipsychotics were equally effective, differing mostly in side effect profile. Newer "atypical" antipsychotics (including risperidone, olanzapine, and quetiapine) have milder side effects (56) and apparently less risk for movement disorders, including potentially irreversible tardive dyskinesia (57). In some circumstances, they may be more effective (58). It is this mostly favorable side effect profile that has allowed earlier treatment of patients who would otherwise be reluctant to take medications. Atypical antipsychotics are substantially more expensive than their predecessors, however, and are not free of adverse effects. All current atypical antipsychotics can cause marked weight gain, and some studies have reported cases of type II diabetes mellitus (59).

Antipsychotic treatment may need to be changed when side effects occur or response is inadequate. If patients experience unacceptable side effects, particularly extrapyramidal symptoms (EPS), clinicians might consider reducing the dose of the conventional antipsychotic or changing to a newer antipsychotic. Symptoms resistant to one or more conventional antipsychotics are likely to resist other conventional agents (60) and should prompt a switch to a newer agent. Current data suggest that treatment-refractory patients may respond to clozapine (61) and possibly risperidone (62) or olanzapine (63) (the data for the latter two are less convincing), but their comparative efficacy is unclear. Clozapine is currently reserved for treatment-resistant cases because its most serious side effect, a 1% incidence of agranulocytosis, requires weekly blood draws. It is contraindicated in patients with myeloproliferative disorders, granulocytopenia, a history of drug-induced agranulocytosis, severe renal or hepatic disease, or uncontrolled epilepsy.

Patients treated with adequate doses of an antipsychotic usually have reduced acute psychotic symptoms in a few days or weeks; some may require up to 12 weeks of treatment. If a patient does not respond after 4 to 6 weeks, clinicians may check plasma levels for such drugs as haloperidol, fluphenazine, or clozapine, for which data are sufficient to interpret the level (64). If the level shows that the patient is taking the medication, the clinician may choose to increase the dose, add a benzodiazepine, or change to another antipsychotic. Compared with conventional antipsychotics, the relatively high improvement rates for newer antipsychotics, including clozapine, suggest that they are the most effective option (**Figure 5**) (65). Anti-EPS drugs and benzodiazapines rarely can cause misuse or dependence, especially with prolonged use. Adjunctive mood stabilizers, although commonly prescribed, have not been found in controlled studies to improve efficacy.

Updates in Long-Term Strategies

Long-term strategies begin when patients enter a stable or maintenance phase with minimal psychotic

symptoms. This may take from 6 to 18 months, and many patients do not return to their baseline level of functioning. The primary goal is minimizing relapse. A frequent question is whether patients need to continue medication when symptoms have dissipated. In the past, the threat of tardive dyskinesia made discontinuation of medical therapy seem reasonable. However, if, as with mood disorders (66), recurrent psychotic episodes facilitate future episodes with increased severity, the long-term aim of preventing episodes becomes increasingly important. One strategy is to use a fixed low-dose antipsychotic regimen (67, 68). Several groups have shown that intermittent treatment—discontinuing medication and reinstituting it if relapse occurs—is ineffective (69). A potentially safer strategy (20) calls for using a low dose of depot antipsychotic and adding an oral antipsychotic if early signs of relapse appear.

However, dose reduction strategies may not be needed for newer antipsychotics that carry a lower risk for EPS and tardive dyskinesia. Until recently, no controlled, double-blind studies have compared these agents with conventional antipsychotics for long-term maintenance, but early experience indicates that they are effective in long-term treatment (70).

Other important long-term goals include the management of cognitive and negative symptoms in restoring the patient to the highest functioning possible. Newer antipsychotics may be more effective than older drugs in treating cognitive and negative symptoms. Long-term rehabilitation is made more difficult by comorbid substance abuse, which is present in approximately 50% of patients and is associated with poor adherence. Dual diagnosis programs are helpful, if the patient will attend regularly.

Special Challenges and New Directions

Adherence is a special challenge in the treatment of schizophrenia because paranoid symptoms can interfere with the patient's trust of the treating physician and the family. Adherence is helped by two general strategies: educating the patient and family and minimizing side effects.

Periodic individual psychotherapy for the patient, focusing on education and skills to help cope with a demoralizing illness, is important. Similarly, family referral to a consumer organization, such as the National Alliance for the Mentally Ill, is helpful (71). Rehabilitation strategies may be useful for some patients (72).

Outright drug refusal is common in patients with schizophrenia who experience side effects, particularly EPS with older agents (approximately 20% prevalence) (73). Thus, adherence is improved if EPS are minimized by using either a newer antipsychotic or a moderate dose of a conventional drug. In younger patients, who are especially vulnerable to dystonias, anti-EPS medications may be advisable even with the first dose if a high-potency conventional antipsychotic is chosen.

Long-acting depot antipsychotics, which are given intramuscularly every 2 to 4 weeks, can be useful when adherence is poor. Depot medications are currently available only for older antipsychotics (haloperidol and fluphenazine) and are used more commonly in Europe than in the United States. They should be considered in patients who have severe psychotic episodes associated with suicidal or aggressive behaviors, in whom any lapse in treatment could be disastrous. This recommendation is supported by a meta-analysis indicating that relapse rates are reduced in patients treated with depot agents (74).

New directions include developing atypical antipsychotics in intramuscular short-acting and depot forms, as well as new medications that work by novel mechanisms and act primarily at receptors other than the dopamine system.

SUMMARY

We have summarized current guidelines for psychopharmacologic strategies used to treat three serious psychiatric disorders. These guidelines are based on studies clarifying and refining the diagnosis of each disorder, updating and testing effective medication treatments, and defining challenges faced in short- and long-term management. Pharmacologic strategies have become more aggressive for each of these disorders because each is chronic and treatable and recurrences are often disastrous to patients, families, and society (60).

Updated research in the diagnosis and definition of each disorder emphasizes stronger evidence of a biological basis for each, ongoing studies of prevalence showing that the disorders are not rare, and attempts at clarifying important symptom subtypes. Updated short-term goals emphasize rapid alleviation of symptoms,

with trials of adequate dose and duration for each medication. Past medications, with their substantial side effects, were often discontinued as soon as possible. However, current recommendations state that most short-term treatments should continue for at least 6 months and for up to 18 months until symptom remission for schizophrenia. Furthermore, we recommend a discrete, 6- to 9-month period of remission before tapering medications to lower doses in patients with schizophrenia or bipolar disorder or discontinuing medication use in patients with major depression who have had fewer than three episodes.

In long-term treatment, the primary goal is minimizing risk for relapse. Many patients and their families prefer the consequences of lifelong medication to the consequences of discontinuing medication use. We believe that the high cost of lifelong medication is justified by the long-term benefits for the individual and society and by evidence that even expensive medications can save money by reducing relapse and rehospitalization rates (75).

When should treatment be initiated by the nonpsychiatrist? Primary care physicians may consider initiating treatment if the diagnosis is already relatively certain (without comorbid psychiatric conditions, especially substance dependence) and if the patient is compliant. First episodes of psychosis and severe symptoms of any of the three illnesses covered here require psychiatric consultation, as do treatment-resistant cases. It must be stressed that all of these illnesses are associated with substantial morbidity and mortality.

Current research in psychopharmacology has allowed enormous progress in developing rational treatment strategies that are based on controlled studies rather than theoretical biases. It is now crucial that we incorporate these strategies into general clinical practice.

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